Association Between Flow Acceleration in the Carotid Artery and Intracranial Aneurysms

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Objectives—In physiologic pulsatile flow, velocity acceleration is an independent factor determining wall shear stress experienced by the vascular endothelium. The purpose of this study was to evaluate Doppler indices of systolic velocity acceleration in extracranial cerebral vessels and the occurrence of intracranial aneurysms.

Methods—We reviewed medical records and 3.0-T brain magnetic resonance imaging with 3-dimensional time-of-flight magnetic resonance angiography of 1323 adults who underwent health checkups from June 2006 to November 2011, in whom 53 intracranial aneurysms were identified in 45 patients. Doppler ultrasound parameters of the carotid and vertebral arteries were analyzed in these 45 patients with aneurysms and compared with another 45 control participants matched for age and sex. We defined the maximum systolic acceleration (ACC_{max}) as the maximum slope of the early phase of systolic acceleration on the Doppler waveform and the maximum acceleration index (AI_{max}) as the ratio of the ACC_{max} and peak systolic velocity.

Results—The Doppler analysis showed a significantly increased AI_{max} and ACC_{max} in the common carotid artery (CCA), internal carotid artery, and vertebral artery in the aneurysm group. A cutoff 13.89 s^{-1} for the AI_{max} of the CCA had sensitivity of 80% with a negative predictive value of 99% for intracranial aneurysms.

Conclusions—This study suggests that the AI_{max} of the CCA with a cutoff of 13.89 s^{-1} may be an alternative to 3-dimensional time-of-flight magnetic resonance angiography or computed tomographic angiography as a screening tool for intracranial aneurysms. Further prospective studies are needed to validate the diagnostic performance and cost-effectiveness of these indices for screening.

Key Words—aneurysm; carotid ultrasound; intracranial aneurysm; vascular ultrasound; velocity acceleration

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Abbreviations
ACC_{max}, maximum systolic acceleration; AI_{max}, maximum acceleration index; CCA, common carotid artery; CTA, computed tomographic angiography; EDV, end-diastolic velocity; ICA, internal carotid artery; MRA, magnetic resonance angiography; MV, mean velocity; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; PSV, peak systolic velocity; US, ultrasound; VA, vertebral artery

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A ruptured aneurysm is an important cause of hemorrhagic stroke among people of working age.[1] Despite advances in treatment techniques and clinical care, ruptured aneurysms still result in high rates of mortality and morbidity.[2,3] Because an aneurysm often remains asymptomatic or presents with equivocal symptoms before it ruptures, screening asymptomatic patients using noninvasive brain imaging, including brain computed tomographic angiography (CTA) and magnetic resonance angiography (MRA), has been performed in several studies. The incidence of intracranial aneurysms in asymptomatic population was estimated to range from 1.8% to 3.7%.[4–6] Because of the low incidence in asymptomatic patients and the relatively higher cost of brain-imaging studies suitable for detecting aneurysms, the benefits of aneurysm screening in the general population remains unclear.[7] Currently, aneurysm screening with brain CTA/MRA is only recommended for patients with an increased risk of intracranial aneurysms, such as those with a family history of intracranial aneurysms/subarachnoid hemorrhage, autosomal dominant polycystic kidney disease, and coarctation of the aorta.[8]

Transcranial Doppler/color-coded carotid duplex imaging is extensively used to identify abnormalities of the extracranial and intracranial vessels through direct visualization and changes in hemodynamic parameters.[9–11] It is suitable for screening and as a follow-up tool because of its lower cost, noninvasiveness, and accessibility. However, a previous report on direct visualization of intracranial aneurysms by transcranial Doppler/color-coded carotid duplex imaging reported sensitivity of 35% for aneurysms smaller than 5 mm compared to brain CTA.[12] In addition, an inadequate temporal bone window in around 10% of patient who undergo transcranial Doppler imaging further limits the application of direct visualization in screening for aneurysms. Alternatively, ultrasound (US) hemodynamic parameters derived from flow velocity and acceleration have been used to screen for vascular stenosis in renal arteries and arteries of the lower extremities[13,14]; however, no previous study has discussed the use of these parameters in screening for intracranial aneurysms. In physiologic pulsatile flow, vascular endothelial cells receive two different types of shear stimuli: a change in wall shear stress at pulsatile flow onset (determined by flow acceleration) and a subsequent steady shear component (determined by steady flow velocity). in vitro studies suggest that these distinct stimuli regulate endothelial function via independent biomechanical pathways.[15] Because increased wall shear stress is considered crucial for the initiation of an intracranial aneurysm,[16–19] parameters that reflect flow velocity and flow acceleration of the cerebrovascular system may serve as surrogate markers for the possible presence of an intracranial aneurysm. Therefore, this study aimed to evaluate whether carotid Doppler indices of steady velocity and velocity acceleration in carotid vessels could be used as indicators of the presence of intracranial aneurysms.

Materials and Methods

Participants

The Institutional Review Board of the Chang Gung Memorial Hospital Ethics Committee approved this study (approval number 201601100B0). We reviewed the medical records of 1323 adult patients who underwent advanced neurologic health checkups from June 2006 to November 2011 at Chang Gung Memorial Hospital (Linkou, Taiwan). All of the patients underwent brain magnetic resonance imaging and MRA without contrast using a 3.0-T scanner (Siemens AG, Erlangen, Germany). The magnetic resonance imaging slice thickness was 4 mm. A board-certified neurologist and an experienced neuroradiologist reviewed the obtained images. Cerebral aneurysms were detected by direct visualization according to a 3-dimensional time-of-flight MRA protocol. In total, we identified 45 patients with intracranial aneurysms using MRA. For comparison, we selected a control group of 45 individually age- and sex-matched participants who had no aneurysm on magnetic resonance imaging from the patients who underwent the advanced neurologic health checkups. These groups were compared for atherosclerosis risk factors, including hypertension, stroke history, current smoking, alcohol consumption, hyperlipidemia, diabetes mellitus, and a history of cardiac disease.

Figure 1. Measurement of systolic velocity acceleration indices from carotid Doppler US. According to the waveforms of carotid and vertebral arteries, the hemodynamic parameters were derived. AT_{max} was defined as the time duration of maximum acceleration, and ΔV_{max} was defined as the difference in velocity from the beginning of a systole to the end of the maximum acceleration slope.

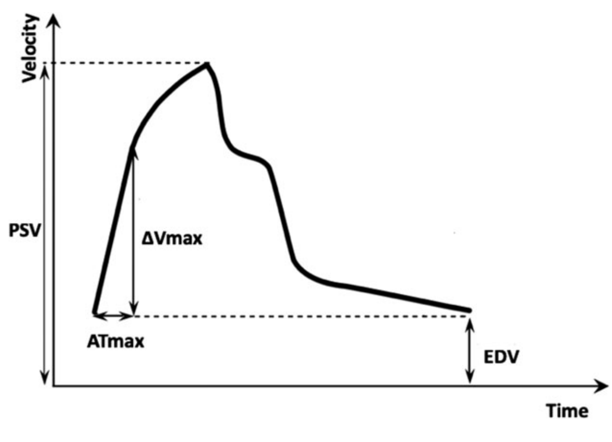
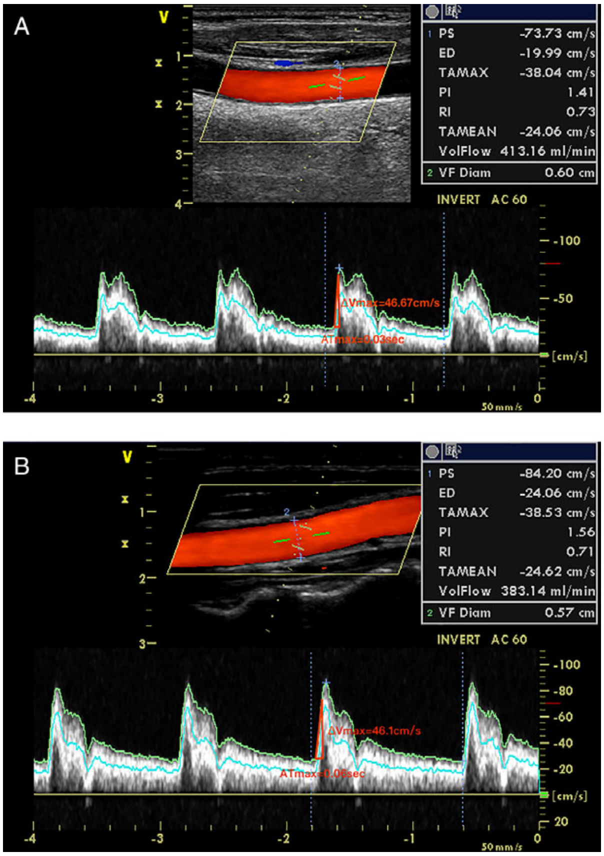


Figure 2. Systolic velocity acceleration indices calculated from information provided by color-coded duplex imaging of the CCA. **A**, The ACC_{max} was 1555 cm/s^2, and the AI_{max} was 21.09 s^{-1} in a 50-year-old woman with a 5-mm aneurysm at the right ICA. **B**, The ACC_{max} was 768 cm/s^2, and the AI_{max} was 9.12 $^{s-1}$ in a 50-year-old woman without an intracranial aneurysm. RI indicates resistive index; TAMAX, time-averaged maximum velocity; TAMEAN, time-averaged mean velocity; VF, Volumetric flow.



Carotid US Imaging and Parameters

We reviewed the US data of the 45 patients with intracranial aneurysms and the 45 matched control participants without aneurysms. All of the Duplex US measurements were performed by a single experienced medical sonographer who specialized in diagnostic neurosonography. The peak systolic velocity (PSV), end-diastolic velocity (EDV), and mean velocity (MV) in the bilateral common carotid arteries (CCAs), internal carotid arteries (ICAs), and vertebral arteries (VAs) from US imaging were obtained with a Vivid 7 Dimension US system (GE Healthcare, Fairfield, CT) equipped with a 9L linear array transducer (frequency range, 2.5–8.0 MHz). In addition, we calculated Doppler parameters, including the maximum systolic acceleration (ACC_{max}), maximum acceleration index (AI_{max}), and pulsatility index (PI) by the following equations: $ACC_{max} = \Delta V_{max}/AT_{max}$; $AI_{max} = ACC_{max}/PSV$; and $PI = (PSV - EDV)/MV$. ACC_{max} was defined as the maximum slope of the early phase of systolic acceleration on the Doppler waveform and AI_{max} as the ratio of ACC_{max} and PSV as proposed by Bardelli et al.[13] AT_{max} was defined as the duration of maximum acceleration and ΔV_{max} as the difference in velocity from the beginning of systole to the end of the maximum acceleration slope (Figure 1). One board-certificated neurologist who was blinded to the clinical information of the participants determined the ACC_{max} and AI_{max}. The measurements of the ACC_{max}, AI_{max},

Figure 3. Box plot showing the distribution of ACC_{max} and AI_{max} of the CCA in the patients with and without intracranial aneurysms. Each symbol at the top is an outlying data point.

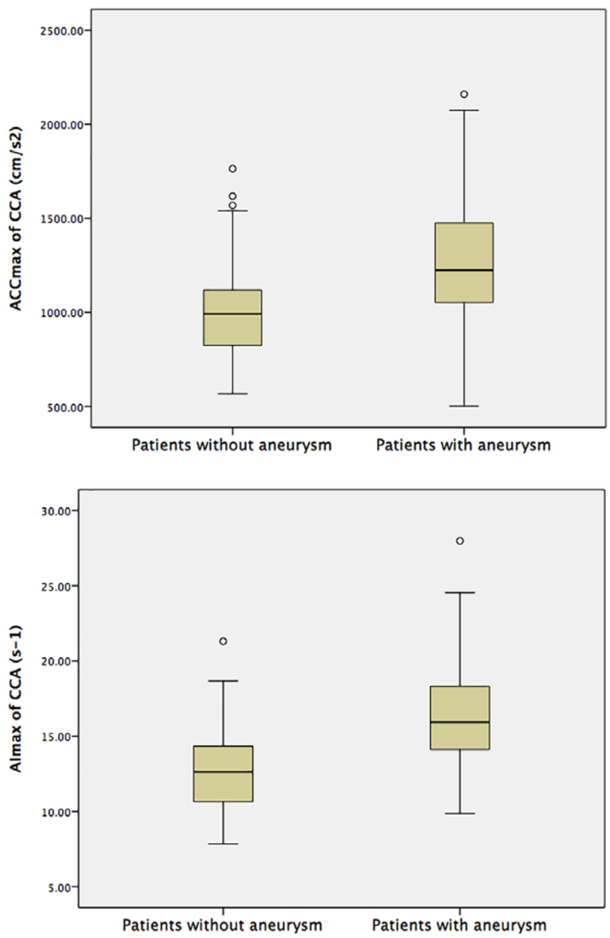


Table 1. Demographic Characteristics of the Patients With Aneurysms and Control Participants for the Doppler Analysis

Characteristic	Aneurysm (n = 45)	Control (n = 45)	*P*
Age, y	60.18 ± 10.974	60.16 ± 10.919	.99
Male/female	15/30	15/30	>.99
Atherosclerosis risk factors			
Hypertension	29	21	.09
Stroke history	3	1	.62
Current smoking	5	3	.71
Alcohol intake	3	3	>.99
Hyperlipidemia	16	8	.06
Diabetes mellitus	8	5	.37
Heart disease	7	6	.76
Symptoms			
Headache	9	10	>.99
Unspecified head discomfort	20	20	>.99
Dizziness	17	11	.26
Fainting history	2	1	>.99

Data are presented as mean ± SD where applicable. Age was compared by the Student *t* test. Categorical variables were compared by the χ^2 or Fisher exact test.

PI, and resistive index from bilateral intracranial vessels were averaged before further analysis.

Statistical Analysis

A 2-tailed Student *t* test was used to compare continuous variables between the participants with and without intracranial aneurysms, including age and carotid US parameters. $P < .05$ was considered to indicate statistical significance. The sensitivity, positive predictive value (PPV), and negative predictive value (NPV) under various levels of specificity were also calculated for each index. All analyses were performed between April 2015 and May 2016 with SPSS version 19 statistical software (IBM Corporation, Armonk, NY).

Results

There were no significant differences in the demographic data between the patients with aneurysms and the control participants (Table 1). A comparison of carotid US parameters between the groups revealed significantly elevated ACC_{max} and AI_{max} values of the CCA, ICA, and VA in the aneurysm

Table 2. Comparison of Carotid US Parameters Between Patients With Aneurysms and Control Participants

Parameter	Aneurysm (n = 45)	Control (n = 45)	P^a
CCA			
ACC_{max}, cm/s^2	1292.90 ± 301.62	999.72 ± 182.25	<.001
AI_{max}, s^{-1}	16.45 ± 2.70	12.70 ± 2.17	<.001
PSV, cm/s	79.81 ± 17.24	80.15 ± 14.77	.92
PI	1.46 ± 0.30	1.45 ± 0.37	.82
ICA			
ACC_{max}, cm/s^2	862.48 ± 251.50	717.72 ± 201.90	.003
AI_{max}, s^{-1}	12.79 ± 5.47	9.78 ± 2.44	.001
PSV, cm/s	71.14 ± 15.55	73.58 ± 11.31	.40
PI	0.95 ± 0.19	0.99 ± 0.25	.30
VA			
ACC_{max}, cm/s^2	845.33 ± 200.20	695.82 ± 200.21	.001
AI_{max}, s^{-1}	16.37 ± 3.46	13.92 ± 3.64	.002
PSV, cm/s	52.53 ± 9.39	50.59 ± 8.27	.30
PI	1.20 ± 0.20	1.52 ± 1.43	.15

Data are presented as mean ± SD.
[a]Two-tailed Student *t* test.

Table 3. Probability Values of Intracranial Aneurysms Under Various Cutoff Limits for ACC_{max} and AI_{max} in the CCA

Parameter	Values				
ACC_{max}					
Cutoff, cm/s^2	1617.99	1465.19	1233.71	1164.35	1086.27
Sensitivity, %	16.7	25.6	48.9	61.1	67.8
Specificity, %	99	95	90	80	70
PPV, %	37	15	15	10	7
NPV, %	35	37	51	59	62
AI_{max}					
Cutoff, s^{-1}	19.03	17.25	16.26	14.68	13.89
Sensitivity, %	23.3	33.3	47.8	66.7	80.0
Specificity, %	99	95	90	80	70
PPV, %	45	19	14	11	9
NPV, %	38	41	50	69	99

group (Table 2). Figure 2 illustrates the measurement of the ACC_{max} and AI_{max} of participants with and without intracranial aneurysms. There were no significant differences in traditional carotid Doppler indices, specifically PSV and PI, between the groups. The distribution of Doppler values in both groups showed less overlap in the AI_{max} of the CCA compared to the ACC_{max} (Figure 3). A cutoff value of 13.89 s^{-1} for the AI_{max} of the CCA yielded sensitivity of 80% with specificity of 70% and an NPV of 99% for intracranial aneurysms. A cutoff value of 1086.27 cm/s^2 for the ACC_{max} of the CCA had sensitivity of 67.8% with specificity of 70% and an NPV of 62% (Table 3).

Discussion

This carotid US study demonstrated that the AI_{max} and ACC_{max} in the extracranial cerebral arteries were correlated with the presence of intracranial aneurysms, with better diagnostic performance in the CCA. The AI_{max} of the CCA with a cutoff value of 13.89 s^{-1} provided substantial sensitivity and a high NPV, which may help clinicians identify patients at a higher risk of having intracranial aneurysms. These indices can easily be calculated from the routinely available information from noninvasive carotid Doppler studies. Our results suggest that the AI_{max} of the CCA obtained from carotid Doppler examinations is potentially useful for screening for intracranial aneurysms.

The reference standard for the detection of intracranial aneurysms is intra-arterial digital subtraction angiography. However, that method is invasive and may be a risk factor for permanent neurologic complications.[20] Therefore, brain MRA and CTA have been widely used to detect the possible presence of intracranial aneurysms for patients presenting with equivocal symptoms or signs of an intracranial aneurysm.[21–23] In a study using contrast-free 3-dimensional time-of-flight MRA at 3.0 T as a screening tool, the accuracy of aneurysm detection reached 98.3% regardless of aneurysm size, which suggested the potential to replace intra-arterial digital subtraction angiography for the diagnosis of intracranial aneurysms.[24] Despite the high sensitivity and specificity provided by these advanced brain-imaging methods, they are costly and include the risk of complications associated with contrast media or repeated exposure to radiation. In a mathematical analysis, MRA screening of asymptomatic patients was shown to be cost-effective only when the 5-year risk of rupture was higher than 13%, as this risk level balanced the cost of MRA and subsequent transarterial embolization for patients with an indication for therapy with the cost of medical care caused by a ruptured aneurysm.[7] In comparison, transcranial Doppler/color-coded carotid duplex imaging has the advantage of a relatively lower cost in screening aneurysms in the general population than MRA. Although direct transcranial Doppler visualization of aneurysms has been reported to have sensitivity of 73% to 78% in some cohorts, the technique is relatively operator dependent, and the sensitivity for aneurysms smaller than 5 mm is poor.[12,25] Moreover, an inadequate temporal bone window in around 10% of patients limits the application of transcranial Doppler imaging for the detection of intracranial aneurysms. In our study, we used information derived from conventional color-coded duplex protocols, which are less operator dependent and not confined to the bone window. The sensitivity reached 80% for the AI_{max} of the CCA for values of greater than 13.89 s^{-1}, with an NPV of 99%. Given the low prevalence of intracranial aneurysms in the general population, the PPV was also expected to be low. The high NPV may help exclude patients less likely to have aneurysms. Because the false-positive rate was 30% at this cutoff limit, further brain imaging studies may be required to confirm the presence of aneurysms for patients suspected of having an aneurysm on color-coded duplex imaging.

In this study, the patients with aneurysms had increased velocity acceleration indices (including AI_{max} and ACC_{max}) in carotid vessels. Pathologically high wall shear stress and a positive wall shear stress gradient in vascular endothelial cells can initiate cascades of biochemical signals within the vessel wall, which can affect vascular wall degradation and aneurysm formation.[16–18] In several human clinical studies, vascular wall shear stress was estimated by using flow velocity based on the Poiseuille law equation.[26,27] However, flow velocity indices have been reported to have a 30% to 50% error in estimating wall shear stress in carotid arteries compared to computational fluid dynamic–derived wall shear stress.[28] An important reason for this error is that velocity-derived wall shear stress estimations cannot capture the change in wall shear stress in pulsatile flow experienced by vascular endothelial cells under physiologic conditions. In a cardiac cycle, vascular endothelial cells receive two different types of shear stimuli, which include a change in shear at the onset of pulsatile flow (determined by flow acceleration) followed by a steady shear component. in vitro studies suggest that these distinct stimuli (velocity acceleration and steady velocity) regulate endothelial function via independent biomechanical pathways.[15] Flow acceleration can affect endothelial function,[19,29,30] mechanotransduction,[31] and the progression of vascular atherosclerosis.[32] Therefore, in addition to steady flow velocity, indices of flow velocity acceleration in the carotid arteries may also help characterize the hemodynamic stress that governs the growth of intracranial aneurysms.

Parameters of systolic upstroke acceleration have been used to evaluate the hemodynamics of both peripheral and carotid blood vessels.[33–38] However, these measures are limited in clinical practice because of variances caused by a late systolic shoulder during the acceleration phase. To improve the accuracy of the estimation of systolic acceleration at flow onset, recent studies have introduced the use of indices of early systolic acceleration. These indices have been found to be superior to traditional Doppler parameters in diagnosing diseases of the peripheral arteries.[13,14] In this study, we evaluated correlations between measures of shear stimuli at the onset of systolic flow in carotid arteries with the occurrence of intracranial aneurysms, so early systolic acceleration indices were probably more suitable measures. The inconsistent correlations between these indices and the presence of aneurysms in VAs could be explained by confounding congenital hypoplasia of VAs in some of our patients.

This study had some limitations. Given the low sample size and retrospective design of this study, further prospective studies with an increased number of patients are needed to validate the diagnostic performance and cost-effectiveness of these color-coded duplex parameters for screening for intracranial aneurysms. Furthermore, multimodality evaluations with techniques including low-velocity flow Doppler US and micro-Doppler US would help validate our hypothesis regarding the correlation between systolic flow acceleration and intracranial aneurysms by a more detailed evaluation of regional blood flow in the intracranial vessels near aneurysm formation.[39,40]

In conclusion, the results of this study show that increased Doppler-derived AI_{max} and ACC_{max} values of the CCA were correlated with the presence of intracranial aneurysms. An AI_{max} value of the CCA exceeding 13.89 s^{-1} had sensitivity of 80% and an NPV of 99% for the presence of intracranial aneurysms. Including these parameters in routine color-coded duplex examinations is a potentially useful screening method for intracranial aneurysms in patients receiving health checkups. Cases suspected of having an aneurysm by color-coded duplex imaging should receive MRA/CTA or digital subtraction angiographic brain imaging studies for confirmation and to assess the possible need for coiling treatment.

Further prospective studies are needed to validate the diagnostic performance and cost-effectiveness of these indices for screening intracranial aneurysms.

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